

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
3 March 2005 (03.03.2005)

PCT

(10) International Publication Number
WO 2005/018651 A1

(51) International Patent Classification⁵: A61K 33/24,
33/00, 9/68, 9/20, 47/26, 47/36, A61J 3/10, A61P 13/12

(21) International Application Number:
PCT/CA2004/001563

(22) International Filing Date: 26 August 2004 (26.08.2004)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:
60/497,560 26 August 2003 (26.08.2003) US
60/517,078 5 November 2003 (05.11.2003) US

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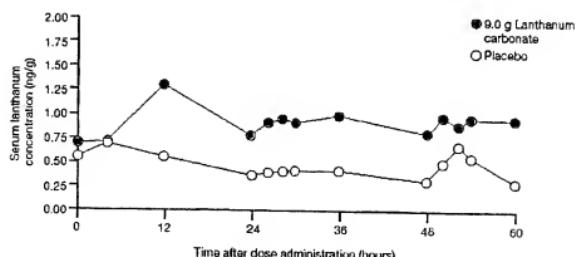
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PI, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: PHARMACEUTICAL FORMULATION COMPRISING LANTHANUM COMPOUNDS



(57) Abstract: This invention relates to a chewable lanthanum formulation comprising a pharmaceutically effective amount of a lanthanum compound; and at least one chewable pharmaceutically acceptable excipient. This invention also relates to a pharmaceutical formulation in a tablet or in a powder comprising a pharmaceutically effective amount of a lanthanum compound produced by a process which comprises the steps of: a) powder blending the lanthanum compound and at least one pharmaceutically acceptable excipient in a mixer to form a mixture; or b) powder blending the lanthanum compound and excipients, compressing the resulting combination into a slug material or roller compacting the resulting combination into a strand material, and milling the prepared material into a free flowing mixture; and c) compressing the resulting mixture into a tablet or filling up the resulting mixture in an appropriate container.

WO 2005/018651 A1



Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette

PHARMACEUTICAL FORMULATION COMPRISING LANTHANUM COMPOUNDS

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BACKGROUND

Hyperphosphataemia is a particular problem of patients with chronic renal insufficiency using dialysis equipment and with about 70% of patients with end stage renal disease (ESRD). This condition can lead to severe bone problems and

10 metastatic calcification of major organs and is associated with significant morbidity and mortality. Conventional dialysis fails to reduce the levels of phosphate in the blood, so that levels rise in time. Elevated phosphate levels are treated using a combination of dietary restrictions and phosphate-binding agents.

15 Another problem of patients with chronic renal insufficiency is secondary hyperparathyroidism. It is also important in patients with chronic renal insufficiency to avoid and treat secondary hyperparathyroidism.

20 Certain forms of lanthanum carbonate have been used to treat hyperphosphataemia in patients with renal failure (see, e.g., JP 1876384). U.S. Patent No. 5,968,976 describes the preparation and use in a pharmaceutical composition of certain hydrates of lanthanum carbonate for the treatment of hyperphosphataemia.

25

SUMMARY OF THE INVENTION

Due to their renal problems patients with end stage renal disease or chronic kidney diseases need to limit their liquid intake. There is therefore a need for a formulation of a lanthanum compound that can be taken with no or limited
30 amount of liquid. There is also a need for a chewable formulation. There is also a need for a formulation that is palatable to the patient especially under conditions

as dry as possible. There is also a need for a formulation that is compressible into a tablet.

This invention relates to a chewable lanthanum formulation comprising:

- 5 a) a pharmaceutically effective amount of a lanthanum compound; and
- b) at least one chewable pharmaceutically acceptable excipient.

This invention relates to a palatable lanthanum formulation comprising:

- 10 a) a pharmaceutically effective amount of a lanthanum compound; and
- b) at least one pharmaceutically acceptable excipient, the formulation being palatable to a mammal, e.g., humans, cats, dogs, etc.

This invention relates to a sprinklable lanthanum formulation comprising:

- 15 a) a pharmaceutically effective amount of a lanthanum compound; and
- b) at least one pharmaceutically acceptable excipient.

This invention relates to a method for controlling hyperphosphataemia in a patient comprising administering a therapeutically effective amount of a lanthanum compound in a palatable formulation.

- 20 This invention relates to a method for controlling hyperphosphataemia in a patient comprising administering a therapeutically effective amount of a lanthanum compound in a chewable formulation.

- 25 This invention relates to a method for controlling hyperphosphataemia in a patient comprising administering a therapeutically effective amount of a lanthanum compound in a sprinklable formulation.

This invention relates to a pharmaceutical formulation in a tablet or in a powder comprising a pharmaceutically effective amount of a lanthanum compound produced by a process which comprises the steps of:

- 5 a) powder blending the lanthanum compound and at least one pharmaceutically acceptable excipient in a mixer to form a mixture and;
- b) compressing the mixture into a tablet or filing up the resulting mixture in an appropriate container.

This invention relates to a pharmaceutical formulation in a tablet or in a powder comprising a pharmaceutically effective amount of a lanthanum compound produced by a process which comprises the steps of:

- 10 a) powder blending the lanthanum compound and at least one pharmaceutically acceptable excipient in a mixer to form a mixture; or
- 15 b) powder blending the lanthanum compound and excipients, compressing the resulting combination into a slug material or roller compacting the resulting combination into a strand material, and milling the prepared material into a free flowing mixture; and
- 20 c) compressing the mixture into a tablet or filing up the resulting mixture in a appropriate container.

This invention relates to a pharmaceutical formulation in a tablet or in a powder comprising a pharmaceutically effective amount of a lanthanum compound produced by a process which comprises the steps of compressing the lanthanum compound into a slug material or roller compacting into a strand material, and 25 milling the prepared material into a free flowing material, then blending with excipients, the resulting combination is compressed into a tablet or filing up the resulting mixture in a appropriate container.

30 In a preferred aspect, such formulation is also chewable and/or sprinklable and/or palatable and the lanthanum carbonate is in a desired hydration state.

This invention relates to a pharmaceutical formulation in a chewable tablet comprising a pharmaceutically effective amount of a lanthanum compound produced by a process which comprises the steps of:

- 5 a) powder blending the lanthanum compound and at least one pharmaceutically acceptable excipient in a mixer to form a mixture; and
b) compressing the mixture into a tablet.

This invention relates to a process for preparing a formulation of a lanthanum compound which comprises the steps of:

- 10 a) powder blending the lanthanum compound and at least one pharmaceutically acceptable excipient in a mixer to form a mixture.

This invention relates to a process for preparing a tablet formulation of a lanthanum compound which comprises the steps of:

- 15 a) powder blending the lanthanum compound and at least one pharmaceutically acceptable excipient in a mixer to form a mixture; and
b) compressing the mixture into a tablet.

20 In one aspect, the present invention is directed to a process for obtaining the formulation of the present invention. It should be noted that the hydration state of the lanthanum compound present in the formulation of the present invention is relevant to the biological properties of the product. It is therefore desirable to maintain a stable hydration status of the lanthanum compound. For example,
25 when the starting lanthanum compound is lanthanum carbonate as defined herein, it is desired to maintain hydration levels constant throughout the formulation process. This represents an additional challenge to obtaining a tablet or powder that is acceptable to the patient. It is important to mention that certain lanthanum compounds, such as lanthanum carbonate have poor flow characteristics. These
30 poor flow characteristics also represent a further challenge when preparing

formulations that have high drug load, as is the case for lanthanum carbonate while maintaining a dose size that is acceptable and palatable to the patient. With drugs which have a specific hydration status, granulating with water or solvents and drying is not always advisable as this can affect the hydration status of the

5 drug. In some cases other techniques such as roller compaction/sludging/milling/compression may be used to improve the flow. If roller compaction/sludging/milling/compression is not suitable, direct compression can be used to make tablets. Again, if the drug has poor flow characteristics and is in a high dose, then direct compression can be difficult due

10 to poor flow. If drug is in low dose(for example 100mg/tablet or less), then a higher proportion of excipients can be used to ameliorate the flow problems but for lanthanum carbonate hydrate, where the drug is present in higher yield, the amount of excipients added must be limited to ensure the tablet is a suitable size. Therefore, there is a need for a formulation process in which allows maintaining

15 the hydration status of the lanthanum compound within desired ranges. In a further embodiment, the process does not require the use of a wet granulation step. In a further embodiment, the formulation process of the present invention does not involve a drying step.

20 In one embodiment, the invention relates to such a method for treating hyperphosphataemia in a renal failure patient, including but not limited to a patient receiving dialysis and a patient with end-stage renal disease (ESRD), comprising administering a therapeutically effective amount of a lanthanum compound.

25 In one embodiment, the invention relates to such a method for treating a chronic kidney disease patient comprising administering a therapeutically effective amount of a lanthanum compound.

In another embodiment, the invention relates to a method for controlling hyperparathyroidism in a patient with chronic renal insufficiency comprising administering a therapeutically effective amount of a lanthanum compound, preferably lanthanum carbonate.

5

In yet another embodiment, the invention relates to a method for treating hyperparathyroidism in a patient with chronic renal insufficiency comprising administering a therapeutically effective amount of a lanthanum compound, preferably lanthanum carbonate.

10

In another embodiment, the lanthanum compound is administered in such a formulation such that plasma levels of lanthanum are low, e.g., at least as good as those provided by a mean concentration curve where C_{max} , T_{max} and AUC are preferably less than 1.5 ng/ml, about 12 hours, and less than 50 ng·hr/ml, respectively, for a dose of 3g per day (e.g., 1g three times a day), such as is achieved in the prior art. In a more preferred embodiment, C_{max} and AUC are less than 1.1 ng/ml and less than 32 ng·hr/ml, and in a most preferred embodiment, C_{max} and AUC are less than 0.5 ng/ml and less than 20 ng·hr/ml, of such dosage. T_{max} values are essentially unaffected by dose and C_{max} and AUC values vary linearly with dosage. All of these parameters have their highly conventional meanings.

15

In another embodiment, the invention relates to a method of treating hyperphosphataemia comprising administering to a patient in need thereof such a lanthanum carbonate formulation.

20

Preferred lanthanum compounds include lanthanum carbonate compounds. Lanthanum carbonate compounds refer to all forms of lanthanum carbonate.

In a preferred embodiment, the invention relates to lanthanum carbonate of the general formula:



where x has a value from 3 to 8, from 3 to 7, from 3 to 6, preferably from 3 to 5,

5 more preferably from 3 to 4, more preferably from 3 to 4.5, preferably from 4 to 5, most preferably 3.4, most preferably x has an average value of 4; for the preparation of a medicament for the treatment of hyperphosphataemia by administration into the gastrointestinal tract; see e.g., U.S. Patent No. 5,968,976 which is incorporated herein by reference. The hydration level of the lanthanum
10 compound can be measured by methods well known in the art, such as thermal analysis (TGA).

In one aspect, the excipients used in the formulation of the present invention are suitable for administration to renally impaired patients. In a further aspect, the

15 excipients include diluents, binders, and lubricants/glidants. It is understood that other agents such as disintegrant, colors, flavors/sweeteners can be added to the formulation.

The diluents can be chosen from dextrose, corn syrup, oligosaccharide,

20 isomaltooligosaccharide, glucose, lycasin, xylitol, lactitol, erythritol, mannitol, isomaltose, polydextrose, dextrin, starch, fructose, xylitol, maltodextrin, maltitol, isomalt, lactose, sorbitol, microcrystalline cellulose (such as avicel), sucrose based diluent-binders (such as Nutab, Di-Pac or Sugartab), confectioner's sugar, calcium sulfate dihydrate, calcium lactate trihydrate, hydrolysed starches (such as
25 Emdex or Celutab), dextrose (such as Cerelose), inositol, hydrolyzed cereal solids (such as Maltrons or Mor-Rex), amylose or glycine.

The diluents can be chosen from dextrose, starch, lactose, mannitol, sorbitol,

30 microcrystalline cellulose (such as avicel), sucrose based diluent-binders (such as Nutab, Di-Pac or Sugartab), confectioner's sugar, calcium sulfate dihydrate,

calcium lactate trihydrate, hydrolysed starches (such as Emdex or Celutab), dextrose (such as Cerelose), inositol, hydrolyzed cereal solids (such as Maltrons or Mor-Rex), amylose or glycine.

5 In a further embodiment, the diluents can be chosen from dextrates, starch, lactose, mannitol, sorbitol, microcrystalline cellulose (such as avicel), sucrose based diluent-binders (such as Nutab, Di-Pac or Sugartab), calcium sulfate dihydrate, calcium lactate trihydrate, hydrolysed starches (such as Emdex or Celutab), dextrose (such as Cerelose), inositol, or amylose.

10 In a further embodiment, the diluent is chosen from dextrates, fructose, xylitol, erythritol, maltodextrin, dextrose, maltitol, isomalt or glucose.

In a further embodiment, the diluent is dextrates.

15 In a further embodiment, lubricant/glidants and blending/flow agents can be chosen from for example magnesium stearate, talc, polyethylene glycol, silica, colloidal anhydrous silica, hydrogenated vegetable oils, glyceryl behenate or glyceryl monostearate.

20 In a further embodiment, lubricant/glidants and blending/flow agents can be chosen from for example magnesium stearate, talc, polyéthylène glycol, silica or colloidal anhydrous silica

25 In one aspect the invention is directed to a chewable formulation comprising:

Formulation	wt % range from about to about
Lanthanum (elemental)	5-50
Diluent(s) (e.g., dextrose (hydrated))	10-90
Blending/flow agent(s)-Lubricant(s) (e.g., colloidal anhydrous silica and/or magnesium stearate)	0.1-6.0

In a further aspect, the invention is directed to a formulation comprising:

5

Formulation	wt % range from about to about
Lanthanum (elemental)	10-40
Diluent(s) (e.g., dextrose (hydrated))	40-80
Blending/flow agent(s)-Lubricant(s) (e.g., colloidal anhydrous silica and/or , magnesium stearate)	0.1-5.0

In a further aspect, the invention is directed to a chewable formulation comprising:

10

Formulation	wt % range from about to about
Lanthanum (elemental)	20-30
Diluent(s) (e.g., dextrates (hydrated))	30-60
Blending/flow agent(s)-Lubricant(s) (e.g., colloidal anhydrous silica and/or , magnesium stearate)	0.1-5.0

In a further aspect, the invention is directed to a formulation comprising:

Formulation	wt % range from about to about
Lanthanum (elemental)	20-30
Diluent(s) (e.g., dextrates (hydrated))	30-50
Blending/flow agent(s)-Lubricant(s) (e.g., colloidal anhydrous silica and/or , magnesium stearate)	0.1-5.0

5

In a further aspect, the invention is directed to a formulation comprising:

Formulation	wt % range from about to about
Lanthanum (elemental)	10-30
Diluent(s) (e.g., dextrates (hydrated))	24-60
Blending/flow agent(s)-Lubricant(s) (e.g., colloidal anhydrous silica and/or magnesium stearate)	0.1-5.0

In a further aspect, the invention is directed to a formulation comprising:

Formulation	wt % range from about to about
Lanthanum (elemental)	20-30
Diluent(s) (e.g., dextrates (hydrated))	40-60
Blending/flow agent(s)-Lubricant(s) (e.g., colloidal anhydrous silica and/or , magnesium stearate)	0.1-5.0

5 In a further aspect, the invention is directed to a chewable formulation comprising:

Formulation	wt % range from about to about
Lanthanum (elemental)	20-27
Diluent(s) (e.g., dextrates (hydrated))	42-58
Blending/flow agent(s)-Lubricant(s) (e.g., colloidal anhydrous silica and/or , magnesium stearate)	0.1-4.0

These formulations are also sprinklable when manufactured in a conventional, applicable dosage form, e.g. beads, crushed tablets, powder, sieved granules, all are palatable. For patients that have a hard time chewing tablets, the formulation can either sprinkled onto a spoon or onto food if needed.

Tablets may be coated according to methods well known in the art.

It may be advantageous to incorporate an antioxidant, for example ascorbic acid, butylated hydroxyanisole or hydroquinone in the formulations of the invention to enhance their storage life.

5 Alternatively, administration may be conducted in an uninterrupted regimen; such a regimen may be a long term regimen, e.g. a permanent regimen.

In one aspect the invention is directed to a pharmaceutical formulation in a tablet containing an amount of elemental lanthanum selected from 250 mg, 500mg, 750 10 mg and 1000mg, produced by a process which comprises the steps of:

15 a) dry admixing a lanthanum compound and excipient in a mixer to form a mixture; and
b) compressing the mixture into tablets using a single punch or rotary tablet machine.

A typical dosage for an adult may be, e.g., 750mg-3000mg daily. The dose can be divided and taken with each meal, for example 250-1000mg, e.g., three times per day. Serum plasma levels can be monitored weekly until an optimal serum 20 phosphate level is reached conventionally.

Lanthanum is a rare earth element with an atomic number of 57. The properties of lanthanum make this agent a good candidate as a useful phosphate binder. It has a high affinity for binding phosphorous and in the form of its carbonate salt, 25 has a low solubility that limits gastrointestinal absorption. In addition, the phosphate binding is independent of pH, it possesses a low toxic potential based on the LD₅₀, it is palatable, abundant, and has limited effects on serum electrolyte concentrations (Hutchison, AJ et al. (1998) *Perit. Dial. Int.* 18(Suppl 2): S38.

It will be understood that the dosages of formulations and the duration of administration according to the invention will vary depending on the requirements of the particular subject. The precise dosage regime will be determined by the attending physician or veterinary surgeon who will, inter alia, consider factors such as body weight, age and symptoms (if any). The formulations may if desired incorporate one or more further active ingredients.

In a further embodiment, the present invention relates to a veterinary use of a lanthanum compound for the treatment of a non-human animal, e.g. a companion animal suffering from hyperphosphataemia comprising the step of administering a pharmaceutically acceptable amount of a lanthanum compound to such an animal, e.g. a companion animal in need of such treatment.

Oral use of medicaments by animals has been commonly quite difficult, due to reluctance of the animals to ingest tablets, pills or medicated food, especially if the drug has an unpleasant taste or odour. Medicament when administered orally, for example, as tablets, even when mixed with habitual food, is frequently rejected by the animal, and the treatment either cannot be effected or must be applied by force, but only to a restricted and thus usually insufficient and inconsistent extent.

There has been limited success in orally administering medicaments to companion animals. For example, US patent No. 5,824,336 describes the need for a palatable anti-helminthic composition for companion animals and is specifically directed to a chewable tablet composition of flubendazole that is palatable to dogs.

More particularly, veterinary handbooks for cat owners typically caution against breaking up pills into powders. For example, in the Cat Owner's Home Veterinary Handbook by Carlson D.G. et al. (1983, First Edition, Howell Book House Inc.) this point is emphasized on the basis that powders make an unpleasant taste which

is poorly tolerated. Furthermore, it advises that medications specifically intended to be added to a cat's ration can be disguised by adding brewer's yeast, cheese or strong fish oil. This reference work also describes more elaborate ways in which tablet and liquid formulations can be directly administered to a cat and particularly, how the cat is held, the mouth opened and the dosage form placed into the cat's mouth, to ensure consumption.

It is also recognized that controlling the diet in companion animals is more difficult and therefore that controlling the intake of phosphates is comparatively difficult relative to human subjects.

It is also notorious that the sense of smell (strongly correlated with taste) of companion animals is especially acute as compared with human subjects. Accordingly, there exists a need for a palatable agent which can be readily used to treat hyperphosphataemia and control associated hypercalcemia especially in companion animals, including, for example dogs and cats. As renal disease is frequently diagnosed in older cats, improved medications for this disease condition are urgently required for this species.

It has now been discovered that lanthanum compounds can be administered to animals, including companion animals in a palatable amount effective to mitigate hyperphosphataemia. Further, it has been discovered that the degree to which a lanthanum compound is palatable in such animals permits such compounds to be administered in a dosage form in which special coatings, masking components and administration procedures are not required to encourage consumption, especially when put into the animal's food ration. In particular, it has been discovered that lanthanum compounds can be administered to cats in an amount effective to mitigate hyperphosphataemia when in a particulate form for admixture with food.

Accordingly, in one aspect the invention is directed to a method for treating hyperphosphaetemia in a companion animal comprising the step of administering a pharmaceutically acceptable amount of a lanthanum compound to a companion animal in need of such treatment.

5

During the dosing regimen, administration may be effected once or more times per day, for example once, twice, three or four times per day.

Unless otherwise defined, all technical and scientific terms used herein have the
10 same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not
15 intended to be limiting.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred embodiments are, therefore, to be construed as merely
20 illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

BRIEF DESCRIPTION OF THE DRAWINGS

25 Figure 1 shows the mean concentration of lanthanum in serum (lanthanum given at maximally tolerated dose for 72 hours).

Figure 2 shows the mean concentration of inorganic phosphorus in urine.

EXAMPLES

Example 1

Preparation of Lanthanum Carbonate Hydrate Chewable tablets (250 mg, 500mg, 750 mg and 1000mg).

5

The manufacturing process involves sieving and blending the active ingredient with the excipients followed by direct compression. More specifically the steps are as follows for the 250mg and 500mg Formulation A tablets:

- 10 a) Pass the lanthanum carbonate, dextrose and colloidal silicon dioxide through a screen of at least 16-mesh into a suitable blender and blend for about 20 minutes.
- b) Pass the talc (optional) and magnesium stearate through a 30-mesh screen and add to the blender and blend for about 5 minutes.
- 15 c) Compress the blend using standard tooling to the target compression weight.

The following tablets were prepared as generally described in the example:

20 **Table 1A**
Formulation A

Ingredient	250mg tablet	500mg tablet	Function
Active Ingredient			
Lanthanum (III) carbonate hydrate	477.0mg	954.0mg	Active
Other Ingredients			
Dextrose (hydrated)	1247.0mg	2494.0mg	Diluent
Colloidal anhydrous silica	36.0mg	72.0mg	Improve blend/flow
Purified talc	30.0mg	60.0mg	Lubricant/ Glidant
Magnesium stearate	10.0mg	20.0mg	Lubricant
TOTAL	1800mg	3600mg	

Table 1B
Formulation B

5

	250 mg Tablet	500 mg Tablet	750 mg Tablet	1000 mg Tablet
Dosage form	Chewable Tablet	Chewable Tablet	Chewable Tablet	Chewable Tablet
Tablet Diameter	13 mm	18 mm	20 mm	22 mm
Formulation				
Lanthanum (elemental)	250 mg	500 mg	750 mg	1000 mg
Lanthanum carbonate hydrate ¹	477 mg	954 mg	1431 mg	1908 mg
Dextrates (hydrated)	533.2 mg	1066.4 mg	1599.6 mg	2132.8 mg
Colloidal silicon dioxide	21.2 mg	42.4 mg	63.6 mg	84.4 mg
Magnesium stearate	10.6 mg	21.2 mg	31.8 mg	42.4 mg
Total Weight	1042 mg	2084 mg	3126 mg	4168 mg

Example 210 Summary of Studies conducted with Formulation A11 1. Several Studies Summary

The ranges of mean concentrations of lanthanum in plasma obtained at designated time points within several studies in randomized patients among five Phase I/II studies are summarized in Table 2.

Table 2

Study Number	Dose Range of Lanthanum (mg/day)	Duration of Treatment (Weeks)	Range of Mean Plasma Lanthanum Levels (SD), ng/ml
1	375 - 2250 Dose Titration (Part 1)	4	0.16 (0.31) - 0.69 (0.55)*
	375 - 2250 Maintenance Fixed Dose (Part 2)	4	0.39 (0.37) - 0.67 (0.98)*
2	225 - 2250 Fixed Dose Levels	6	0.21 (0.22) - 0.86 (0.91)
3	750 - 3000 Adjustable Dose Levels	49	0.38 (0.25) - 0.67 (0.65)
4	375 - 3000 Dose Titration to Fixed Dose Levels	10	0.35 (0.44) - 0.78 (1.05)
5	750 - 3000 Dose Titration to Fixed Dose Levels	52	0.4 (0.76) - 0.6 (1.15)

* Units are ng/gm. Conversion to ng/ml, multiply plasma concentrations by 1.054, density of plasma.

5 The ranges and the upper range values of the mean plasma lanthanum levels are similar across the PhaseII/III studies with the highest mean level at <1ng/ml. The range values were similarly low as the values of C_{max} that were determined in earlier studies.

10 2. This study evaluates the primary and safety pharmacology of a conventional non-calcium anti-hyperphosphataemia treatment, lanthanum carbonate (LC).

Methods

15 The *in vitro* phosphate binding efficacy of LC is assessed at the relevant gastrointestinal pHs of 3, 5 and 7 using aluminum hydroxide (AH) and calcium-salts as comparators. *In vivo* dietary phosphate binding is compared with AH, calcium carbonate (CC) and sevelamer hydrochloride (SH) (1000 mg binder/kg/day) in 5/6th nephrectomized rats are dosed daily for 6 weeks and using 20 urine phosphate excretion as the primary end-point. The potential for unwanted

pharmacological effects of LC on CNS, cardiovascular, respiratory and GI systems is evaluated in mice, rats and dogs at doses up to 2000 mg/kg/day.

Results

5 *In vitro*, LC is equipotent with AH and significantly more potent than CC or calcium acetate. LC is most effective (97.5% phosphate bound) at pH 3, but also has good efficacy at pH 5 and 7. In 5/6th nephrectomized rats, LC is equipotent with AH and significantly more potent than CC or SH at reducing urinary phosphate excretion, a sensitive marker of dietary phosphate binding in
10 this model. At doses up to 2000 mg/kg, LC has no direct effects on serum calcium, vitamin D or PTH levels and no adverse pharmacological actions on cardiovascular, respiratory or GI systems in mice, rats or dogs. No acute or long-term effects on CNS function occur in mice or dogs in Irwin and neurotoxicity screens. LC has no pro- or anti-convulsive activity and no effects on locomotor
15 activity in mice.

This study indicates that LC is a selective and potent phosphate binder with similar efficacy to aluminum hydroxide and a low potential for adverse safety pharmacology.

20 3. This preclinical study is conducted to investigate the long-term toxicity of conventional lanthanum carbonate (LC).

Methods

25 Single- and multiple-dose oral and iv toxicity studies with LC in mice, rats and dogs use doses up to 2000 mg/kg/day (po) (x17 a human dose of 1000 mg t.i.d.) and 1 mg/kg/day (iv). Plasma LC levels are up to 20,000 times those in dialysis patients. The studies range in duration up to 1 year in dogs and 2 years (life-time exposure) in rodents. Studies in 5/6th nephrectomized rats evaluated
30 any influence of renal impairment on the toxicity profile. The studies include

clinical assessments, ECG, ophthalmoscopy, haematology, urinanalysis, serum chemistry, plasma and tissue LC exposure, and histopathological examination of over 40 tissues. Full programs to assess genetic toxicity, reproduction toxicity and carcinogenicity are also conducted.

5

Results

LC is very well tolerated, with no effects on appearance, growth or survival in the life-time studies. Adaptive changes in the rodent stomach (not observed in dogs) are the only findings at high oral doses. Rats with impaired renal function have comparable tissue exposure to normal rats, and also tolerate LC very well. Histomorphometry reveals no potential for direct bone toxicity. Some indirect effects on mineralization are due to phosphate depletion caused by excessive dietary binding at high doses. Lanthanum is not genotoxic or carcinogenic, and does not adversely affect any stage of reproduction.

10

4. This study is conducted to compare conventional lanthanum carbonate (LC) with other therapies (calcium or aluminum salts, or sevelamer hydrochloride).

15

Methods

This 2-year multicenter, randomized, open-label, parallel-group trial consists of a 1- to 3-week washout period, a 6-week titration phase and a long-term maintenance phase. Hemodialysis patients with serum phosphorus > 5.9 mg/dL (> 1.9 mmol/L) receive either LC (375–3000 mg/day elemental lanthanum) or their pre-study phosphate binder. The primary aim of the study is to evaluate safety and tolerability over 2 years. The main efficacy endpoint is control of serum phosphorus ≤ 5.9 mg/dL.

Results

In total, 647 patients receive LC and 642 receive standard therapy (calcium agents: 78%; sevelamer: 16%). Average total treatment exposure is higher with standard therapy than with LC (422.2 ± 258.5 vs. 304.1 ± 253.8 days).

5 Treatment-emergent adverse events occur with greater frequency in the standard therapy group than the LC group included hypercalcemia (10.4 vs. 3.4%), diarrhea (27.4 vs. 19.8%), abdominal pain (20.9 vs. 14.1%) and dyspepsia (14.8 vs. 8.2%). Serious adverse events are also more frequent in the standard-treatment group (65.4 vs. 51.0%). However, this is likely to be complicated by
10 the difference in treatment exposure between groups. Plasma lanthanum remains very low throughout treatment (mean level: 0.5–0.6 ng/mL). Similar proportions of patients in both groups have effective phosphorus control during maintenance therapy (46.3% vs. 41.3%; standard therapy vs. LC at 2 years).

15 LC is at least as well tolerated as other current phosphate binders over the long term, and exhibits similar efficacy in maintaining serum phosphate control over a 2-year period.

5. This study compares the efficacy, safety and tolerability of conventional
20 lanthanum carbonate (LC) with those of calcium carbonate (CC) in a randomized, open-label, multicenter trial.

Methods

25 After a 1- to 3-week washout period, haemodialysis patients with hyperphosphataemia (serum phosphorus > 1.80 mmol/L [5.6 mg/dL]) are randomized to receive LC (375–3000 mg/day lanthanum; n = 533) or CC (1500–9000 mg/day calcium; n = 267). Patients are then titrated to a maintenance dose of either drug that provides optimal phosphate control (serum phosphorus < 1.80 mmol/L) within 5 weeks. Both LC- and CC-treated patients who have controlled

serum phosphorus levels after titration receive maintenance treatment for 20 weeks more.

Results

5 Control of serum phosphorus levels is achieved in similar proportions of patients treated with LC and CC (Week 9: 67.9% vs. 65.8%; Week 25: 65.8% vs. 63.9%). LC is associated with a significantly greater decrease in calcium x phosphorus product than CC at Week 9 (-1.80 vs. -1.35 mmol²/L²; P = 0.009) and a numerically greater decrease at Week 25 (-1.59 vs. -1.26 mmol²/L²).
10 Plasma levels of lanthanum are very low throughout treatment with LC: 0.49 ng/mL at the highest lanthanum dose administered at Week 25. Adverse events are generally mild or moderate in severity, occurring in 77.7% of patients receiving LC and 79.8% of patients receiving CC. Hypercalcaemia occurs substantially more frequently in patients receiving CC (20.2%) compared with
15 those receiving LC (0.4%).

LC shows equivalent efficacy to CC in controlling serum phosphorus in patients with end-stage renal disease. LC is well tolerated, with a lower risk of hypercalcaemia than CC.

20 6. This study reports the results from a 6-month, open-label extension of a previous 6-month, randomized clinical trial comparing conventional LC with calcium carbonate (CC).

25 *Methods*

Following 6 months of randomized treatment in the initial trial, patients who receive CC for 6 months are switched to a 5-week titration with LC (CC/LC group) to control serum phosphorus at ≤ 1.8 mmol/L (5.6 mg/dL). Those who initially receive LC in the randomized trial continue to receive LC at their established maintenance dose (LC/LC group; total treatment duration, 49 weeks).

Results

In total, 518 patients entered the extension study: 185 in the CC/LC group and 333 in the LC/LC group. Overall, 375 patients (72.4%) completed the study:
5 113 (61.1%) in the CC/LC group and 262 (78.7%) in the LC/LC group. Serum phosphorus levels are maintained at around 1.8 mmol/L (5.6 mg/dL) in both groups over 24 weeks: mean endpoint values were 1.76 mmol/L in the LC/LC group and 1.83 mmol/L in the CC/LC group. At the end of the extension period,
10 serum phosphorus is controlled in 63.3% of the LC/LC group, compared with 58.3% of the CC/LC group. The most common treatment-emergent adverse events are gastrointestinal, while those considered to be related to study treatment are reported by 17% of LC/LC patients and 31% of CC/LC patients. Hypercalcemic episodes are reported by 0.3% of patients in the LC/LC group and
15 2.7% of patients in the CC/LC group.

15

LC is well tolerated and effective for a period of at least 1 year. The reduced incidence of hypercalcemia observed with LC in short-term trials is maintained for 1 year.

20 7. Safety and efficacy are assessed in a large-scale, randomized, 1-year trial of the effects of prolonged treatment with conventional lanthanum carbonate (LC) or calcium carbonate (CC) on bone parameters.

Methods

25 Chronic renal failure patients undergoing haemodialysis or continuous ambulatory peritoneal dialysis are randomized (1:1) to receive either LC (up to 3750 mg/day lanthanum; n = 49) or CC (up to 9000 mg/day calcium; n = 49) for 50 weeks. Safety analyses include adverse events, vital signs and plasma lanthanum. Efficacy assessments include serum phosphorus and parathyroid hormone (PTH).

Results

All 98 patients were included in the intent-to-treat efficacy and safety population. Adverse-event profiles were similar with LC and CC, but hypercalcemic events (serum calcium > 2.65 mmol/L) were much less frequent with LC (6%) than with CC (35%). There were no clinically relevant changes in vital signs during LC or CC therapy. Plasma lanthanum levels were similar in the LC- and CC-treated patients (range, 0.31–0.11 ng/mL) at baseline, and were higher in LC-treated patients (< 0.03–1.95 ng/mL) than in CC-treated patients (all 5 < 0.03 ng/mL) at endpoint. Plasma lanthanum reached steady state early in the study in LC-treated patients, and was similar between Weeks 8 and 52. LC and CC provided similar control of serum phosphorus. Baseline mean (\pm SD) values were 1.72 ± 0.39 and 1.87 ± 0.52 mmol/L, and endpoint values were 1.79 ± 0.47 and 1.65 ± 0.54 mmol/L with LC and CC, respectively. Serum PTH remained 10 stable with LC over 1 year, but decreased with CC.

LC appeared to be equally well tolerated and showed equivalent efficacy to CC, but with a greatly reduced risk of hypercalcemia over 1 year of treatment. As in other long-term studies, prolonged LC therapy did not result in plasma 15 lanthanum accumulation.

8. This study evaluated the efficacy and safety of conventional lanthanum carbonate (LC) in an ethnic Chinese population. LC tablets providing 500 mg lanthanum were evaluated. These higher-strength tablets could reduce overall pill burden – an important issue affecting patient compliance.

Methods

The study comprised 3 parts: a 1- to 3-week screening and washout phase, a 4-week, open-label, dose-titration phase with LC, and a 4-week, double-blind, 25 maintenance phase in which patients were randomized (1:1) to receive LC or

placebo. LC was administered as chewable tablets providing 250 or 500 mg lanthanum. Male and female haemodialysis patients were included who had serum phosphorus levels > 5.6 mg/dL (1.8 mmol/L) following washout of their previous phosphate binder. The study enrolled 103 patients. The primary efficacy endpoint 5 was the serum phosphorus level obtained at the last week of double-blind treatment. The control of serum phosphorus to ≤ 5.6 mg/dL (1.8 mmol/L) was the main secondary efficacy endpoint. Other secondary efficacy measures included the profile of serum phosphorus during titration, and serum parathyroid hormone, calcium and calcium × phosphorus product levels. The safety and tolerability 10 profile of LC was assessed by monitoring of adverse events and vital signs at each study visit. Full biochemical and haematological screens were also undertaken, and plasma levels of lanthanum were measured throughout the study.

9. Renal osteodystrophy (ROD) is an important complication of 15 hyperphosphataemia, associated with significant patient morbidity. Aluminum-based phosphate binders have been associated with bone toxicity and have thus added to the existing difficulties of ROD. This study was designed to demonstrate the lack of similar toxicity for conventional lanthanum carbonate (LC) and to compare its long-term effects on bone with those of calcium carbonate (CC).
20

Methods

In total, 98 patients were randomized to treatment with either LC (n = 49) or CC (n = 49) for 1 year. Tetracycline-labeled bone biopsies were taken at baseline and after 1 year of open-label treatment, and full histomorphometry 25 analyses performed. Bone alkaline phosphatase activity and serum parathyroid hormone (PTH) and calcitriol levels were also measured.

Results

Bone biopsies from baseline and following 1 year of treatment were 30 available from 33 LC- and 30 CC-treated patients. Neither group demonstrated

aluminum-like bone toxicity. After 1 year, 5/7 LC- and 3/7 CC-treated patients with osteomalacia or adynamic bone at baseline, and 4/5 LC- and 3/6 CC-treated patients with high-turnover ROD at baseline had evolved away from these severe types of ROD. Only one patient in the LC group evolved towards adynamic bone vs. six in the CC group. There were no significant differences in bone alkaline phosphatase activities or serum calcitriol levels between the treatment groups or at the end of the study (vs. baseline). Serum PTH levels remained stable in the LC group, whereas reductions were seen in the CC group, with a greater variation in data range.

10

Over 1 year, dialysis patients treated with LC showed a greater evolution away from the more severe types of ROD compared with CC-treated patients. Other parameters of bone status showed no significant change in LC-treated patients. LC may therefore have an advantage over conventional phosphate binders when treating ROD.

15 The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of the invention for those used in the preceding examples.

20

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A chewable lanthanum formulation in a tablet comprising a pharmaceutically effective amount of a lanthanum compound and at least one chewable pharmaceutically acceptable excipient.
5
2. The chewable formulation of claim 1 wherein said tablet contains more than about 200mg of elemental lanthanum.
3. The chewable formulation of claim 1 wherein said tablet contains more than about 250mg of elemental lanthanum.
- 10 4. The chewable formulation of claim 1 wherein said tablet contains about 250mg of elemental lanthanum.
5. The chewable formulation of claim 1 wherein said tablet contains more than about 500 mg of elemental lanthanum.
- 15 6. The chewable formulation of claim 1 wherein said tablet contains about 500 mg of elemental lanthanum.
7. The chewable formulation of claim 1 wherein said tablet contains more than about 750 mg of elemental lanthanum.
8. The chewable formulation of claim 1 wherein said tablet contains about 750 mg of elemental lanthanum.
- 20 9. The chewable formulation of claim 1 wherein said tablet contains more than about 1000 mg of elemental lanthanum.
10. The chewable formulation of claim 1 wherein said tablet contains about 1000 mg of elemental lanthanum.
- 25 11. The chewable formulation of claim 1 wherein said tablet contains from about 200 mg of elemental lanthanum to about 1000mg.
12. The chewable formulation according to any one of claims 1 to 11 wherein said lanthanum compound is lanthanum carbonate.
13. The chewable formulation according to any one of claims 1 to 11 wherein said lanthanum compound is lanthanum carbonate of the general formula:
30 $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$

where x has a value from 3 to 8.

14. The chewable formulation of claim 13 wherein x has a value from 3 to 7.

15. The chewable formulation of claim 13 wherein x has a value from 3 to 6.

5 16. The chewable formulation of claim 13 wherein x has a value from 3 to 5.

17. The chewable formulation of claim 13 wherein x has a value from 4 to 5

18. The chewable formulation of claim 1 wherein the excipient is chosen from
the group consisting of diluents and blending flow-lubricant agents.

10 19. The chewable formulation of claim 18 wherein which comprises at least
one diluant selected from the group consisting of dextrates, corn syrup,
oligosaccharide, isomaltoligosaccharide, glucose, lycasin, xylitol, lactitol,
erythritol, mannitol, isomaltose, polydextrose, dextrin, starch, fructose,
15 xylitol, maltodextrin, maltitol, isomalt, lactose, sorbitol, microcrystalline
cellulose, sucrose based diluent-binders, confectioner's sugar, calcium
sulfate dihydrate, calcium lactate trihydrate, hydrolysed starches, dextrose
inositol, hydrolyzed cereal solids, amylose and glycine.

20 20. The chewable formulation of claim 18 wherein which comprises at least
one diluant selected from the group consisting of dextrates, starch, lactose,
mannitol, sorbitol, microcrystalline cellulose, sucrose based diluent-
binders, confectioner's sugar, calcium sulfate dihydrate, calcium lactate
trihydrate, hydrolysed starches, dextrose, inositol, hydrolyzed cereal
25 solids, amylose and glycine.

21. The chewable formulation of claim 18 which comprises at least one
diluant selected from the group consisting of diluents can be chosen from
dextrates, starch, lactose, mannitol, sorbitol, microcrystalline cellulose,

sucrose based diluent-binders, calcium sulfate dihydrate, calcium lactate trihydrate, hydrolysed starches, dextrose, inositol, and amylose.

22. The chewable formulation of claim 18 which comprises at least one
5 diluent selected from the group consisting of dextrates, fructose, xylitol,
erythritol, maltodextrin, dextrose, maltitol, isomalt and glucose.

23. The chewable formulation of claim 18 wherein the diluent is dextrates.

10 24. The chewable formulation according to any one of claims 1 to 11 which
comprises dextrates as a diluent in an amount from about 10% to about
90% by weight based on the total weight of all ingredients.

15 25. The chewable formulation according to claim 12 which comprises
dextrates as a diluent in an amount from about 10% to about 90% by
weight based on the total weight of all ingredients.

20 26. The chewable formulation according to claim 13 which comprises
dextrates as a diluent in an amount from about 10% to about 90% by
weight based on the total weight of all ingredients.

25 27. The chewable formulation according to any one of claims 1 to 11 which
comprises dextrates as a diluent in an amount from about 40% to about
80% by weight based on the total weight of all ingredients.

28. The chewable formulation according to claim 12 which comprises
dextrates as a diluent in an amount from about 40% to about 80% by
weight based on the total weight of all ingredients.

29. The chewable formulation according to claim 13 which comprises dextrates as a diluent in an amount from about 40% to about 80% by weight based on the total weight of all ingredients.
- 5 30. The chewable formulation according to any one of claims 1 to 11 which comprises dextrates as a diluent in an amount from about 30% to about 60% by weight based on the total weight of all ingredients.
- 10 31. The chewable formulation according to claim 12 which comprises dextrates as a diluent in an amount from about 30% to about 60% by weight based on the total weight of all ingredients.
- 15 32. The chewable formulation according to claim 13 which comprises dextrates as a diluent in an amount from about 30% to about 60% by weight based on the total weight of all ingredients.
- 20 33. The chewable formulation according to any one of claims 1 to 11 which comprises dextrates as a diluent in an amount from about 40% to about 60% by weight based on the total weight of all ingredients.
- 25 34. The chewable formulation according to claim 12 which comprises dextrates as a diluent in an amount from about 40% to about 60% by weight based on the total weight of all ingredients.
- 30 35. The chewable formulation according to claim 13 which comprises dextrates as a diluent in an amount from about 40% to about 60% by weight based on the total weight of all ingredients.
36. The chewable formulation of claim 18 which comprises blending flow agents-lubricating agents selected from the group consisting of magnesium

stearate, talc, polyethylene glycol, silica, colloidal anhydrous silica, hydrogenated vegetable oils, glyceryl behenate and glyceryl monostearate.

37. A pharmaceutical formulation in a tablet or in a powder comprising a
5 pharmaceutically effective amount of a lanthanum compound produced by a process which comprises the steps of:

- a. powder blending the lanthanum compound and at least one pharmaceutically acceptable excipient in a mixer to form a mixture; or
- 10 b. powder blending the lanthanum compound and excipients, compressing the resulting combination into a slug material or roller compacting the resulting combination into a strand material, and milling the prepared material into a free flowing mixture; and
- c. compressing the mixture into a tablet or filling up the resulting mixture in a appropriate container.

15 38. A pharmaceutical formulation in a tablet or in a powder comprising a pharmaceutically effective amount of a lanthanum compound produced by a process which comprises the steps of compressing the lanthanum compound into a slug material or roller compacting into a strand material, and milling the prepared material into a free flowing material, then blending with excipients, the resulting combination is compressed into a tablet or filling up the resulting mixture in a appropriate container.

20 25 39. A pharmaceutical formulation in a chewable tablet comprising a pharmaceutically effective amount of a lanthanum compound produced by a process which comprises the steps of:

- a. powder blending the lanthanum compound and at least one pharmaceutically acceptable excipient in a mixer to form a mixture; and

b. compressing the mixture into a tablet.

40. A method for treating hyperphosphataemia comprising administering a therapeutically effective amount of a lanthanum formulation according to any one of claims 1 to 39 to a patient in need of thereof.

5 41. The use of a therapeutically effective amount of a lanthanum formulation according to any one of claims 1 to 39 for treating hyperphosphataemia in a patient in need thereof.

10

42. A process for preparing a tablet formulation of a lanthanum compound which comprises the steps of:

15 a. powder blending the lanthanum compound and at least one pharmaceutically acceptable excipient in a mixer to form a mixture; and

 b. compressing the mixture into a tablet.

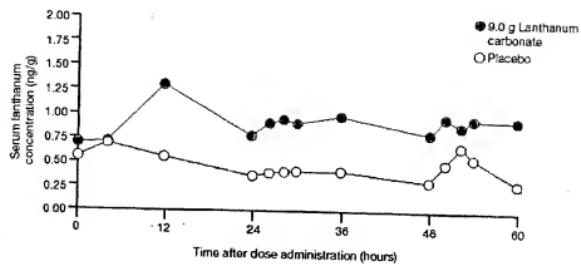


FIGURE 1

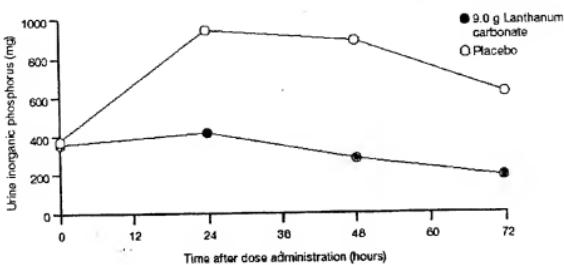


FIGURE 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/001563

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K-33/24, 33/00, 9/68, 9/20, 47/26, 47/36; A61J-3/10; A61P-13/12

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K-33/24, 33/00, 9/68, 9/20, 47/26, 47/36; A61J-3/10; A61P-13/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base, and, where practicable, search terms used)
Canadian Patent Database (CPD), PubMed, EPOLINE, Internet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CA 2216437C (Murrer & Powell) 3 October 1996 (3.10.1996) page 1, lines 3-5; page 3; page 11, lines 15 - page 12, line 6.	1-42
Y	Encyclopaedia of Pharmaceutical Technology, Eds. J. Swarbrick & J.C. Boylan), Volume 2 (1990) "Biodegradable polyester polymers as drug carriers to clinical pharmacokinetics and pharmacodynamics"; "Chewable tablets" pages 397-417; page 397, 1 st paragraph; page 404, 2 nd paragraph; pages 406-409.	19-23, 24-35
Y	Encyclopaedia of Pharmaceutical Technology, Eds. J. Swarbrick & J.C. Boylan), Volume 14 (1996); "Self-medication to technology transfer considerations for pharmaceuticals"; Formulation design" pages 391-399. page 392, Table 1.	37-39, 42
A	Hutchison, A. J. Calcitriol, lanthanum carbonate, and other new phosphate binders in the management of renal osteodystrophy, Perit Dial Int, Volume 12, Suppl 2 1999, 408-12. whole document	1, 12-17, 40, 41

Further documents are listed in the continuation of Box C.

Patent family members are listed in annex.

- * Special categories of cited documents :
 - "A" document defining the general state of the art which is not considered to be of particular relevance
 - "E" earlier application or patent but published on or after the international filing date
 - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 - "O" document referring to an oral disclosure, use, exhibition or other means
 - "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and in conflict with the application but cited to understand the prior art necessary for appreciating the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international-type search 10 December 2004 (10-12-2004)	Date of mailing of the international-type search report 19 January 2005 (19-01-2005)
Name and mailing address of the ISA/ Commissioner of Patents Canadian Patent Office - PCT Ottawa/Gatineau K1A 0C9 Facsimile No. 1-819-953-9358	Authorized officer Maja Solajic (819) 956-4121

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/001563

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)	
<p>This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :</p> <ol style="list-style-type: none"> 1. <input checked="" type="checkbox"/> Claims Nos.: 40 because they relate to subject matter not required to be searched by this Authority, namely: Although claim 40 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. 2. <input type="checkbox"/> Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically : 3. <input type="checkbox"/> Claims Nos.: because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). 	
Box III Observation where unity of invention is lacking (Continuation of item 3 of first sheet)	
<p>This International Searching Authority found multiple inventions in this international application, as follows :</p> <ol style="list-style-type: none"> 1. <input type="checkbox"/> As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims. 2. <input type="checkbox"/> As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee. 3. <input type="checkbox"/> As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos. : 4. <input type="checkbox"/> No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos. : 	
<p>Remark on Protest</p> <p><input type="checkbox"/> The additional search fees were accompanied by the applicant's protest. <input type="checkbox"/> No protest accompanied the payment of additional search fees.</p>	

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2004/001563

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2216437	03-10-1996	AT209923T T AU702073 B2 AU4951496 A BR9607926 A CA2216437 A1 CN1102393B B CZ293494 B6 DE69617659D D1 DE69617659T T2 DK817639T T3 EA270 B1 EE4096 B1 EP0817639 A1 ES2170223T T3 GB9506126D D0 HK1008182 A1 HU9900799 A2 JP3224544B2 B2 NO3134888 B1 NZ303265 A PL184315B B1 PT817639T T SI817639T T1 SK128897 A3 TR9701030T T1 TW436288 B US5968976 A WO9630029 A1 ZA9602369 A	15-12-2001 11-02-1999 16-10-1996 09-06-1998 03-10-1996 05-03-2003 12-05-2004 17-01-2002 02-10-2002 02-04-2002 25-02-1999 15-08-2003 14-01-1998 01-08-2002 10-05-1998 11-10-2002 28-09-1999 29-10-2001 14-10-2002 28-01-2000 31-10-2002 31-05-2002 30-06-2002 07-10-1998 22-06-1998 28-05-2001 19-10-1999 03-10-1996 18-11-1996

